ClinicalEvidence

Organophosphorus poisoning (acute)

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ABSTRACT

INTRODUCTION: Acetylcholinesterase inhibition by organophosphorus pesticides or organophosphate nerve agents can cause acute parasympathetic system dysfunction, muscle weakness, seizures, coma, and respiratory failure. Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for acute organophosphorus poisoning? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 62 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: activated charcoal (single or multiple doses), alpha$_2$ adrenergic receptor agonists, atropine, benzodiazepines, butyrylcholinesterase replacement therapy, cathartics, extracorporeal clearance, gastric lavage, glycopyrronium bromide (glycopyrrolate), ipecacuanha (ipecac), magnesium sulphate, milk or other home remedy immediately after ingestion, N-methyl-D-aspartate receptor antagonists, organophosphorus hydrolases, oximes, removing contaminated clothes and washing the poisoned person, and sodium bicarbonate.

QUESTIONS

INTERVENTIONS

TREATMENTS

Footnote

*Based on consensus, RCTs would be considered unethical.

Key points

- Acetylcholinesterase inhibition by organophosphorus pesticides or organophosphate nerve agents can cause acute parasympathetic system dysfunction, muscle weakness, seizures, coma, and respiratory failure.

  Prognosis depends on the dose and relative toxicity of the specific compound, as well as pharmacokinetic factors.

- Initial resuscitation, then atropine and oxygen, are considered to be the mainstays of treatment, although good-quality studies to show benefit have not been found.

  The optimum dose of atropine has not been determined, but common clinical practice is to administer sufficient to keep the heart rate >80 bpm, systolic blood pressure above 80 mmHg, and the lungs clear.

  Glycopyrronium bromide may be as effective as atropine in preventing death, with fewer adverse effects, although no adequately powered studies have been done.

- Removing contaminated clothes and then washing the poisoned person is a sensible approach, but no studies have been reported that evaluate benefit.

  Healthcare workers should ensure that washing does not distract them from other intervention priorities, and should protect themselves from contamination.

- Benzodiazepines are considered to be standard treatment to control organophosphorus-induced seizures, although we found no specific studies.

- It is not known whether activated charcoal, alpha$_2$ adrenergic receptor agonists (clonidine), butyrylcholinesterase replacement therapy using fresh frozen plasma or plasmapheresis, magnesium sulphate, N-methyl-D-aspartate receptor antagonists, organophosphorus hydrolases, sodium bicarbonate, milk and other "home remedies" taken soon after ingestion, cathartics, or extracorporeal clearance improve outcomes.

  Oximes have not been shown to improve outcomes, but most studies have been of poor quality so a definite conclusion cannot be made.

  Potential benefits from gastric lavage or ipecacuanha are likely to be outweighed by the risks of harm, such as aspiration.

Clinical context

DEFINITION

Acute organophosphorus poisoning occurs after dermal, respiratory, or oral exposure to either low volatility pesticides (e.g., chlorpyrifos, dimethoate) or high volatility nerve agents (e.g., sarin, tabun). Inhibition of acetylcholinesterase at synapses results in accumulation of acetylcholine and overactivation of acetylcholine receptors at the neuromuscular junction and in the autonomic and central nervous systems. [1] Early clinical features (the acute cholinergic crisis) reflect involvement of the parasympathetic system and include bronchorrhoea, bronchospasm, miosis, salivation, defecation, urination, and hypotension. Features indicating involvement of the neuromuscular junction (muscle weakness and fasciculations) and central nervous system (seizures, coma, and respiratory failure) are common at this stage. Respiratory failure may also occur many hours later, either separated in time from the cholinergic crisis (intermediate syndrome [2]) or merged into the acute cholinergic crisis. [3] The pathophysiology of this late respiratory failure seems to involve downregulation of nicotinic acetylcholine receptors. [2] [3] Intermediate syndrome is particularly important since people who are apparently well can progress rapidly to respiratory arrest. A late motor or motor/sensory peripheral neuropathy can develop after recovery from acute poisoning with some organophosphorus pesticides. [1] Acute poisoning may result in long-term neurological and psychiatric effects but the evidence is still unclear. [4] [5] There are differences between pesticides in the clinical syndrome they produce and in the frequency and timing of respiratory failure and death. [3] [6] [7]

INCIDENCE/ PREVALENCE

Most cases occur in the developing world as a result of occupational or deliberate exposure to organophosphorus pesticides. [8] Although data are sparse, organophosphorus pesticides seem to be the most important cause of death from deliberate self poisoning worldwide, causing about 200,000 deaths each year. [9] For example, in Sri Lanka, about 10,000 to 20,000 admissions to hospital for organophosphorus poisoning occur each year. Of these, at least 10% die. In most cases, the poisoning is intentional. [10] Case mortality across the developing world is commonly >20%. [9] In Central America, occupational poisoning is reported to be more common than intentional poisoning, and deaths are fewer. [11] Deaths from organophosphorus nerve agents occurred during the Iran–Iraq war [12] and military or terrorist action with these chemical weapons remains possible. Twelve people died in a terrorist attack in Tokyo and several thousands died in Iran following military use.

AETIOLOGY/ RISK FACTORS

The widespread accessibility of pesticides in rural parts of the developing world makes them easy options for acts of self harm. [9] Occupational exposure is usually because of insufficient or inappropriate protective equipment. [8]

PROGNOSIS

There are no validated scoring systems for categorising severity or predicting outcome of acute organophosphorus poisoning. The highly variable natural history and difficulty in determining the dose and identity of the specific organophosphorus compound ingested make predicting outcome for an individual person inaccurate and potentially hazardous, because people admitted in good condition can deteriorate rapidly and require intubation and mechanical ventilation. Prognosis in acute self poisoning is likely to depend on dose and toxicity of the organophosphorus compound that has been ingested (e.g., neurotoxicity potential, half life, rate of ageing, whether activation to a toxic compound is required (e.g., parathion to paraoxon [pro-poison]), and whether it is dimethylated or diethylated [see comment on oximes, p 10]). [7] [13] Prognosis in occupational exposure is better because the dose is normally smaller, the route is dermal, and the compound more easily identified.

AIMS OF INTERVENTION

To prevent mortality; to reduce rates of intubation (with or without ventilation), pneumonia, and delayed polyneuropathy; and to reduce the duration of ventilation and intensive care.

OUTCOMES

Mortality; pneumonia; intermediate syndrome; delayed polyneuropathy; rates of intubation, and duration of ventilation or intensive care.

METHODS

Clinical Evidence search and appraisal April 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2010, Embase 1980 to April 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, and cohort studies in any language, including "open" (non-blinded) RCTs, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. The contributor also searched Medline, Embase, and Cochrane databases; hand searched toxicological and Indian journals (search date 2010); and contacted experts in the field to identify unpublished studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions in this review (see table, p 17).The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for acute organophosphorus poisoning?

OPTION ATROPINE

Mortality

Compared with glycopyrronium bromide We don't know if atropine and glycopyrronium bromide differ in their effectiveness at reducing mortality in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (low-quality evidence).

Need for ventilation

Compared with glycopyrronium bromide We don't know if atropine is more effective than glycopyrronium bromide at reducing the proportion of people with acute organophosphorus poisoning who require ventilation, as we found insufficient evidence from one small RCT (low-quality evidence).

Pneumonia

Compared with glycopyrronium bromide We don't know if atropine is more effective than glycopyrronium bromide at reducing respiratory infection rates in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (very low-quality evidence).

Note

We found no RCTs or cohort studies comparing atropine versus placebo. Consensus holds that the effectiveness of atropine is beyond question, so it would be unethical to perform an RCT. Many case series found that atropine reversed the early muscarinic effects of acute organophosphorus poisoning. Atropine and oxygen are the mainstays of treatment for acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits:

Atropine versus placebo:
We found no systematic review, RCTs, or cohort studies (see comment below). Many case series found that atropine reversed the early muscarinic effects of acute organophosphorus poisoning. [14]

Atropine versus glycopyrronium bromide:
See benefits of glycopyrronium bromide, p 4 .

Harms:

We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving atropine (see comment below). Excessive treatment with

atropine results in toxicity, characterised by confusion and tachycardia. [14] In hypoxic people, supplemental oxygen may reduce the risk of atropine-induced ventricular tachycardias.

Comment: Atropine competes with excess acetylcholine at muscarinic acetylcholine receptors.

Clinical guide:
Although we found no RCTs, consensus holds that the effectiveness of atropine is beyond question, so it would be unethical to perform an RCT comparing atropine versus placebo. Atropine and oxygen are the mainstays of treatment for acute organophosphorus poisoning. Sufficient atropine to stabilise the person should be given rapidly.

Dosage and administration:
The optimum dose of atropine has not been determined. [15] It varies among poisoned people because of variation in the dose and organophosphorus compound taken and possibly because of coadministration of an oxime (oximes have been proposed to have anticholinergic action at high dose; see oximes, p 10). [16] The first doses are given as boluses to reverse the muscarinic signs (0.6–3.0 mg iv depending on severity; in the primary care situation, an autoinjector can be used that supplies 2 mg im). Since organophosphorus deaths result from cardiorespiratory failure, recent Sri Lankan studies have aimed to give sufficient atropine rapidly to improve cardiovascular function (systolic blood pressure >80 mmHg, pulse >80 bpm) and respiratory function (treat bronchorrhoea and bronchospasm). [15] [16] This atropine dose regimen has not been compared with other regimens with different end points of atropinisation. Once the person is loaded with atropine, current recommendations are then to set up an atropine infusion [16] at a dose that aims to maintain cardiorespiratory function (see above) and prevent toxicity (normal bowel sounds, no agitation or confusion). [15] [17] A prospective observational cohort study that examined an ad hoc dosage regimen versus a titrated dosing protocol found more atropine toxicity associated with ad hoc dosing compared with dosing titrated to clinical effect. [18]

OPTION BENZODIAZEPINES

We found no direct information from RCTs or cohort studies about benzodiazepines in the treatment of people with acute organophosphorus poisoning.

Note
It would be considered unethical to perform an RCT of benzodiazepines in people with seizures; consensus holds that benzodiazepines, such as diazepam, lorazepam, and midazolam, should be the preferred treatment for seizures and for agitation. Many case series have reported that diazepam controls seizures in acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or cohort studies. Many case series have reported that diazepam controls seizures in acute organophosphorus poisoning. [19] [20]

Harms: We found no studies of sufficient quality assessing adverse effect rates in people with acute organophosphorus poisoning receiving diazepam. Excessive treatment with diazepam may result in respiratory depression requiring intubation and ventilation. However, this is also a direct complication of organophosphorus poisoning, and it is difficult to distinguish between the two. [19]

Comment: Seizures are believed to be initiated by excess acetylcholine in the brain after inhibition of acetylcholinesterase, with subsequent disruption of other neurotransmitter systems such as glutamate and catecholamines. Benzodiazepines work at gamma-aminobutyric acid receptors. Sufficient atropinisation may help to manage organophosphorus-induced seizures. Routine use of benzodiazepines before any seizure occurs has support from animal models, but we found no studies in humans. [21]

Clinical guide:
Consensus is that benzodiazepines, such as diazepam, lorazepam, and midazolam, should be the preferred treatment for seizures and for agitation, [22] and they are widely used. It would now be considered unethical to perform an RCT comparing benzodiazepines versus placebo in people with seizures.

OPTION GLYCOPYRRONIUM BROMIDE (GLYCOPYRROLATE)

Mortality

Compared with atropine We don't know if glycopyrronium bromide and atropine differ in their effectiveness at reducing mortality in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (low-quality evidence).

Need for ventilation
Compared with atropine We don't know if glycopyrronium bromide is more effective than atropine at reducing the proportion of people with acute organophosphorus poisoning who require ventilation, as we found insufficient evidence from one small RCT (low-quality evidence).

Pneumonia
Compared with atropine We don't know if glycopyrronium bromide is more effective than atropine at reducing rates of respiratory infections in people with acute organophosphorus poisoning, as we found insufficient evidence from one small RCT (very low-quality evidence).

Note
We found no RCTs or cohort studies comparing glycopyrronium bromide (glycopyrrolate) versus placebo. It is unlikely that an RCT would be considered ethical unless glycopyrronium bromide and placebo were given in addition to atropine. Consensus is that glycopyrronium bromide can be used in place of atropine, and it may reduce the risk of confusion caused by treatment. However, glycopyrronium bromide is not widely used and may be less effective than atropine at controlling the central nervous system complications of organophosphorus poisoning. In some regions, glycopyrronium bromide is combined with atropine to limit the central stimulation produced by atropine.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits:

Glycopyrronium bromide versus placebo:
We found no systematic review or RCTs comparing glycopyrronium bromide versus placebo (see comment below).

Glycopyrronium bromide versus atropine:
We found one small RCT (39 people) comparing glycopyrronium bromide versus atropine. [23] It found no significant difference between atropine and glycopyrronium bromide in case fatality, need for ventilation, or respiratory infection rates (AR for case fatality: 1/22 [5%] with atropine *v* 2/17 [12%] with glycopyrronium; RR 0.39, 95% CI 0.04 to 3.91; AR for need for ventilation: 8/22 [36%] with atropine *v* 6/17 [35%] with glycopyrronium; RR 1.03, 95% CI 0.44 to 2.41; AR for respiratory infection rates: 12/22 [55%] with atropine *v* 5/17 [29%] with glycopyrronium; RR 1.86, 95% CI 0.81 to 4.25). The study may have lacked power to detect clinically important differences in mortality, ventilation, or intermediate syndrome.

Harms:

We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving glycopyrronium bromide. Treatment with glycopyrronium bromide may result in peripheral anticholinergic effects such as tachycardia, dry mouth, and ileus. [24] When these symptoms arise, treatment is defined as excessive.

Comment:

It is unlikely that an RCT comparing glycopyrronium bromide versus placebo would be considered ethical unless glycopyrronium bromide and placebo were given in addition to atropine. Glycopyrronium bromide has similar pharmacological effects to atropine in humans, but is more selective for peripheral cholinergic synapses, resulting in less tachycardia and confusion than occur with atropine. [24] Animal studies found that glycopyrronium bromide was less effective than atropine at controlling bradycardia and central nervous system complications of organophosphorus poisoning. We found no large RCT comparing atropine versus glycopyrronium bromide.

Clinical guide:
Consensus is that glycopyrronium bromide can be used in place of atropine, and it may reduce the risk of confusion caused by treatment. However, glycopyrronium bromide is not widely used and may be less effective than atropine at controlling the central nervous system complications of organophosphorus poisoning. In some regions, glycopyrronium bromide is combined with atropine to limit the central stimulation produced by atropine.

OPTION REMOVING CONTAMINATED CLOTHES AND WASHING THE POISONED PERSON

We found no direct information from RCTs or cohort studies about removing contaminated clothes and washing the poisoned person in people with acute organophosphorus poisoning.

Note
Although we found no RCTs or high-quality observational studies comparing removal of contaminated clothes and washing versus placebo, this seems to be an obvious way to reduce further dermal and mucocutaneous exposure and is widely recommended. An RCT would therefore be considered unethical. Consensus

is that the poisoned person should be disrobed and washed carefully once initial resuscitation has been performed and they are stable, and after administration of oxygen and atropine as required. Early removal of clothing seems empirically to be an effective contribution to decontamination. Healthcare workers should protect themselves carefully against contamination.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality. No important adverse effects are envisaged, unless disrobing and washing the poisoned person distracts healthcare workers from other priorities, such as resuscitation and careful observation for deterioration.

Comment: **Clinical guide:**
Absorption of organophosphorus compounds through the skin varies, according to the volatility of the organophosphorus, its vehicle solvent, and the temperature and hydration of the skin. [25] Absorption of pesticides seems to be low, with studies of malathion, chlorpyrifos, and diazinon suggesting that <5% is absorbed and excreted in the urine. [26] [27] [28] However, disrobing and washing seems to be an obvious way to reduce further dermal and mucocutaneous exposure and is widely recommended. An RCT would therefore be considered unethical. Consensus is that the poisoned person should be disrobed and washed carefully once initial resuscitation has been performed and they are stable, and after administration of oxygen and atropine as required. Healthcare workers should protect themselves through the use of gloves, aprons, and eye protection, with careful disposal of contaminated equipment and clothes.

OPTION ACTIVATED CHARCOAL (SINGLE OR MULTIPLE DOSE)

Mortality
Activated charcoal (single or multiple dose) compared with no charcoal We don't know whether single-dose activated charcoal or multiple-dose activated charcoal are more effective than no charcoal at reducing mortality in people with acute organophosphorus poisoning (moderate-quality evidence).

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found two non-systematic reviews [29] [30] and one subsequent RCT. [31]

The first non-systematic review found no human studies examining the effects of single-dose activated charcoal (SDAC) specifically in people with organophosphorus poisoning. [29] In people with other forms of poisoning, it found no evidence of benefit. [29]

The second non-systematic review found no human studies examining the effects of multiple-dose activated charcoal (MDAC) specifically in people with organophosphorus poisoning. [30] In people with other forms of poisoning, it found no evidence of benefit. [30]

The subsequent open-label RCT (4632 people, in 3 Sri Lankan hospitals, 97% of people presented within 24 hours of ingestion, median time between ingestion and hospital admission 4.2 hours) compared MDAC (1533 people), SDAC (1545 people), and no charcoal (1554 people) in adults with self poisoning who were receiving otherwise standard treatment. [31] However, the RCT included several different forms of self poisoning and did not report overall results for organophosphorus poisoning alone. It reported a prespecified subgroup analysis for people with organophosphorus pesticide or carbamate pesticide poisoning (1310/4632 [28%] people). The RCT found no significant difference between either MDAC or SDAC versus no charcoal in all-cause mortality during hospital admission (poison suspected organophosphorus or carbamate pesticide: MDAC *v* no charcoal, 870 people; OR 0.78, 95% CI 0.51 to 1.19; SDAC *v* no charcoal, 881 people; OR 0.94, 95% CI 0.63 to 1.41). However, these figures included people with carbamate pesticide poisoning. In a further subgroup analysis (reported in web tables) in people with organophosphorus pesticide poisoning, the RCT found no significant difference between MDAC or SDAC versus no charcoal when analysed by the type of organophosphorus poisoning (MDAC *v* no charcoal: poison suspected diethyl organophosphorus: 7/144 [5%] with MDAC *v* 12/135 [9%] with no charcoal; OR 0.52, 95% CI 0.20 to 1.37; dimethyl organophosphorus: 16/121 [13%] with MDAC *v* 27/155 [17%] with no charcoal; OR 0.72, 95% CI 0.37 to 1.41; unknown: 9/58 [16%] with MDAC *v* 9/44 [20%] with no charcoal; OR 0.71, 95% CI 0.26 to 1.98; SDAC *v* no charcoal: poison suspected diethyl organophosphorus: 14/141 [10%] with SDAC *v* 12/135 [9%] with no charcoal; OR 1.13, 95% CI 0.50 to 2.54; dimethyl organophosphorus: 25/127 [20%] with SDAC *v* 27/155 [17%] with no charcoal; OR 1.16, 95% CI 0.64 to 2.12; unknown: 4/48 [8%] with SDAC *v* 9/44 [20%] with no charcoal; OR 0.35, 95% CI 0.10 to 1.24). [31]

Harms: The subsequent RCT reported that overall, for all forms of acute poisoning, that none of the people who died during the study had substantial quantities of charcoal in their lungs at post mortem. [31] Overall, for all forms of poisoning, it reported that the proportion of people with absent bowel sounds were small (1.1% with MDAC *v* 0.5% with SDAC *v* 1.1% with no charcoal; statistical analysis between groups not reported), and there was a small non-significant increase in seizures in people receiving either regimen of charcoal compared with no charcoal (1.4% with MDAC *v* 1.6% with SDAC *v* 0.5% with no charcoal; MDAC *v* no charcoal, OR 3.15, 95% CI 0.61 to 16.18; SDAC *v* no charcoal, OR 3.44, 95% CI 0.70 to 16.81). [31] Adverse effects of activated charcoal may include aspiration, pneumonia, vomiting, diarrhoea, constipation, ileus, and reduced absorption of oral medication. [29] [30] [32] A large retrospective case series (878 people treated with MDAC) suggests that rates of adverse events with multiple-dose regimens (>2 doses) are likely to be low (significant pulmonary aspiration in 6/878 [0.6%], 95% CI 0.1% to 1.1%). [33]

Comment: Animal studies indicate that activated charcoal can bind to organophosphorus pesticides. [34]

Clinical guide:
In people who have taken a large amount of pesticide and are seen within 1 hour, consensus is that a single dose of activated charcoal may offer benefit after gastric lavage.

OPTION ALPHA2 ADRENERGIC RECEPTOR AGONISTS

We found no direct information from RCTs or cohort studies about alpha$_2$ adrenergic receptor agonists in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving clonidine. Adverse effects of clonidine may include sedation, hypotension, bradycardia, and (with prolonged use) rebound hypertension. [35]

Comment: Clonidine inhibits the release of acetylcholine from cholinergic neurones and has alpha$_2$ adrenergic agonist effects. Animal studies found that pretreatment with clonidine improves survival after organophosphorus poisoning; combination with atropine was more than additive. [36] This treatment has not yet been studied in organophosphorus poisoning in humans.

Clinical guide:
There is currently insufficient evidence to recommend the use of clonidine in people with organophosphorus poisoning.

OPTION BUTYRYLCHOLINESTERASE REPLACEMENT THERAPY

We found no direct information from RCTs or cohort studies about butyrylcholinesterase replacement therapy (such as with fresh frozen plasma or plasmapheresis) in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found one systematic review (search date 2002) of the effectiveness of fresh frozen plasma, but it found no RCTs in people with acute organophosphorus poisoning. [37] We found one non-systematic review of the effectiveness of plasmapheresis, but it did not report on its use in people with acute organophosphorus poisoning. [38]

Harms: Neither review found any good-quality RCTs reporting adverse effects of butyrylcholinesterase replacement therapy in people with acute organophosphorus poisoning. [37] Serious adverse effects associated with treatment include transfusion-associated lung injury [39] and hypotension. [38]

Comment: The rationale behind the use of fresh frozen plasma or plasmapheresis in people with organophosphorus poisoning is that they may reduce high blood pesticide concentrations by increasing plasma levels of the enzyme butyrylcholinesterase (plasmapheresis may also remove some poison if the responsible organophosphorus pesticide has a small volume of distribution, see extracorporeal clearance, p 8). Organophosphorus pesticides bind to and inhibit butyrylcholinesterase in plasma, reducing the amount of pesticide available to inhibit the more clinically important acetylcholinesterase. However, since butyrylcholinesterase is generally sensitive to organophosphorus pesticides, it is usually rapidly used up in moderate to severe poisoning. Replacement of butyrylcholinesterase by administration of fresh frozen plasma or by plasmapheresis

should increase the level of enzyme in the blood and neutralise some pesticide. However, whether sufficient butyrylcholinesterase can be given to produce clinical benefit is unknown. A small controlled study (12 people given plasma and 21 people not given plasma) has reported benefit of fresh frozen plasma but it was not an RCT and allocation decisions were unclear. [40] The same researchers reported raised plasma butyrylcholinesterase activity in one poisoned person after plasmapheresis. [41] Since these sources of butyrylcholinesterase are reasonably affordable and available, it is important to determine whether butyrylcholinesterase replacement therapy is effective. One study (in Chinese, with only the abstract available in English) suggested that butyrylcholinesterase activity in fresh frozen plasma falls rapidly and that such plasma should be used within 1 day of donation. [42] Further studies are required to confirm this finding. Use of fresh frozen plasma or plasmapheresis risks transmission of viral and bacterial infectious agents. Careful screening of blood for known pathogens will reduce but not remove this risk. Other sources of butyrylcholinesterase, such as recombinant butyrylcholinesterase, are under development.

Clinical guide:
There is currently insufficient evidence to recommend the use of butyrylcholinesterase replacement therapy in people with organophosphorus poisoning.

OPTION EXTRACORPOREAL CLEARANCE

We found no direct information from RCTs or cohort studies about extracorporeal clearance in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality to assess adverse effects of extracorporeal clearance in organophosphorus poisoning.

Comment: Effectiveness of extracorporeal clearance will be affected by the volume of distribution of each organophosphorus poison, which is likely to correlate with lipid solubility. Extracorporeal clearance may therefore have some effect for non-fat soluble organophosphorus poisons, such as dimethoate and methamidophos, but little effect for very lipid-soluble organophosphorus poisons, such as fenthion. Future clinical trials of extracorporeal clearance will need to take this variability into account. A Cochrane systematic review of extracorporeal clearance in organophosphorus pesticide poisoning is currently underway. [43]

Clinical guide:
There is currently insufficient evidence to recommend the use of extracorporeal clearance in people with organophosphorus poisoning.

OPTION GASTRIC LAVAGE

We found no direct information from RCTs or cohort studies about gastric lavage in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: **Gastric lavage versus no gastric lavage:**
We found one systematic review (search date 2006) of gastric lavage in people with acute organophosphorus poisoning. [44] The review found no controlled studies comparing gastric lavage versus no gastrointestinal decontamination in unselected people or in early presentation. It found one non-randomised controlled study that compared gastric lavage versus no gastric lavage in late presentation (>12 hours post ingestion). However, the review reported that it was unclear how people were allocated to an intervention, few study details were given, time to presentation was not reported, and it was unclear whether people had received prior gastric decontamination at a previous (transferring) hospital. We have therefore not reported this study further.

Harms: **Gastric lavage versus no gastric lavage:**
We found no studies of sufficient quality assessing the adverse effects of gastric lavage in people with acute organophosphorus poisoning, and no large, high-quality RCTs comparing gastric lavage versus placebo in any form of poisoning that might allow calculation of rates of adverse effects. Adverse effects of gastric lavage may include aspiration, hypoxia, laryngeal spasm, and oesophageal perforation. [45] Adverse effects are common when gastric lavage is performed in physically restrained, non-consenting people without careful control of the airway.

Comment: One non-systematic review identified no studies examining the effects of gastric lavage specifically in people with organophosphorus poisoning. [45] In people with other forms of poisoning, it found no evidence of benefit. [45] A small cohort study of gastric lavage in non-consenting people poisoned with pesticides or plants has been published. [46]

Clinical guide:
Gastric lavage may delay administration of activated charcoal and specific treatment for organophosphorus poisoning. It is unclear how long organophosphorus pesticides remain in the stomach after ingestion. If future studies indicate that a substantial proportion of organophosphorus remains in the stomach by the time of admission to hospital, it may be appropriate to conduct an RCT to assess gastric lavage (performed as recommended [45]) after protection of the airway. In people who have taken a large amount of pesticide and are seen within 1 to 2 hours, consensus is that careful insertion of a nasogastric tube to drain the stomach and perform a brief gastric lavage may offer benefit in people who consent to this treatment or are unconscious and have had their airway protected.

OPTION MAGNESIUM SULPHATE

We found no direct information from RCTs or cohort studies about magnesium sulphate in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality to assess adverse effects of magnesium sulphate in organophosphorus poisoning. One large, high-quality RCT (10,141 women) of magnesium sulphate in eclampsia (4 g loading dose then 1 g/hour for 24 hours) found few serious adverse effects from magnesium sulphate. [47] The most frequent adverse effects are bradycardia and low blood pressure owing to cardiovascular effects, and respiratory depression, weakness, and loss of deep tendon reflexes in the short term owing to impaired neuromuscular transmission. [48]

Comment: Magnesium sulphate is an inhibitor of acetylcholine release in the central nervous system and at peripheral sympathetic and parasympathetic synapses. [49] The administration of magnesium to animals poisoned with organophosphorus pesticides improves outcome, possibly owing to a favourable effect on neuromuscular junction block or increased hydrolysis of some pesticides. [50] The use of magnesium in acute organophosphorus poisoning in humans has been reported in two small studies. [51] [52] In the first study, intravenous administration of magnesium sulphate 4 g to 4 people produced some improvement in neuromuscular function in two people. [51] The second non-randomised comparative study reported that magnesium decreased mortality compared with usual care (0/11 [0%] with magnesium *v* 5/34 [15%] with usual care; P <0.01). [52] However, the study was very small, allocation was not randomised (every fourth eligible person received magnesium sulphate), and the dose of magnesium sulphate used and other aspects of the methodology were incompletely described in the publication. Therefore, these results should be interpreted with caution.

Clinical guide:
There is currently insufficient evidence to recommend the use of magnesium sulphate in people with organophosphorus poisoning.

OPTION MILK OR OTHER HOME REMEDY SOON AFTER ORAL ORGANOPHOSPHORUS EXPOSURE

We found no direct information from RCTs or cohort studies about giving milk or other home remedy immediately after ingestion in people with acute organophosphorus poisoning.

Note
Consensus is that administration of large amounts of fluid soon after the poisoning should be discouraged.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects.

Comment:

Clinical guide:
The lay practice of giving a "home remedy" soon after ingestion, before bringing the poisoned person to hospital, is common in many parts of the world. Problems may occur when large volumes

of fluid are given "to dilute the poison" or to make the person vomit. Gastric emptying of a fluid is proportional to volume. Therefore, increasing the volume of fluid in the stomach may increase the rate of emptying into the small bowel where the pesticide is absorbed. Giving fluids therefore risks speeding the onset of poisoning and causing respiratory arrest before the person arrives at a healthcare facility. Consensus is that administration of large amounts of fluid soon after the poisoning should be discouraged.

OPTION N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

We found no direct information from RCTs or cohort studies about N-methyl-D-aspartate receptor antagonists in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of adverse effects in people with acute organophosphorus poisoning receiving N-methyl-D-aspartate (NMDA) receptor antagonists. A dose ranging clinical study found that adverse effects of NMDA receptor antagonists include dizziness, vomiting, nausea, stupor, agitation, and hallucinations. [53]

Comment: Primate studies found that treating organophosphorus nerve gas poisoning with NMDA receptor antagonists, such as gacyclidine, improved clinical recovery, reduced neural death, and improved electroencephalogram activity. [54]

Clinical guide:
There is currently insufficient evidence to recommend the use of NMDA receptor antagonists in people with organophosphorus poisoning.

OPTION ORGANOPHOSPHORUS HYDROLASES

We found no direct information from RCTs or cohort studies about organophosphorus hydrolases in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing adverse effects.

Comment: Oxime efficacy is normally limited by the presence of high pesticide concentrations, which reinhibit acetylcholinesterases that have been reactivated by the oximes. [55] A method of rapidly reducing pesticide concentrations could potentially allow oximes to be more effective. Animal studies found that organophosphorus hydrolases (such as mammalian paraoxonase or the bacterial hydrolase isolated from *Pseudomonas* species) cleaved organophosphorus compounds, lowering blood and tissue concentrations of organophosphorus. [56] [57] These may prove beneficial for managing people with either pesticide or nerve agent organophosphorus poisoning.

Clinical guide:
Organophosphorus hydrolases have not yet entered clinical development.

OPTION OXIMES

Mortality
Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing mortality in people with acute organophosphorus poisoning, or whether different regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low-quality evidence).

Need for ventilation
Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing the need for ventilation in people with acute organophosphorus poisoning, or whether different regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low-quality evidence).

Intermediate syndrome

Compared with placebo or no oximes or different regimens versus each other We don't know whether oximes are more effective than placebo or no oximes at reducing intermediate syndrome in people with acute organophosphorus poisoning, or whether different regimens of pralidoxime differ in effectiveness. Evidence was weak, contradictory, and it was difficult to draw reliable conclusions (very low-quality evidence).

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found three systematic reviews [58] [59] [60] and three subsequent RCTs. [61] [62] [63]

The first systematic review (search date 2003) [58] of oximes in people with organophosphorus poisoning identified two RCTs (182 people) of pralidoxime (reported in 4 publications), which reported different comparisons and outcomes meaning that a meta-analysis could not be performed. [64] [65] [66] [67] Neither of the RCTs found any benefit of pralidoxime (see comments below). The first RCT found that, compared with a bolus of pralidoxime 1 g, an infusion of pralidoxime 12 g (no loading dose, given over 4 days) increased mortality, intermediate syndrome, and the need for ventilation (AR for mortality: 8/36 [22%] with pralidoxime 12 g *v* 5/36 [14%] with pralidoxime 1 g; OR 1.77, 95% CI 0.52 to 6.00; AR for intermediate syndrome: 20/36 [56%] with pralidoxime 12 g *v* 13/36 [36%] with pralidoxime 1 g; OR not reported; AR for need for ventilation: 24/36 [67%] with pralidoxime 12 g *v* 17/36 [47%] with pralidoxime 1 g; OR 2.04, 95% CI 0.78 to 5.30); however, confidence intervals were wide, and the difference was not significant. [64] [65] Post-hoc analysis of this RCT suggested that people receiving pralidoxime 1 g in the first 12 hours may be less likely to develop intermediate syndrome than those receiving <1 g in the first 12 hours (29% with pralidoxime 1 g *v* 51% with pralidoxime <1 g; RR 0.58, 95% CI 0.27 to 1.26). [64] The second RCT (110 people) found that an infusion of pralidoxime 12 g over 3 days increased mortality, intermediate syndrome, and requirement for ventilation compare with placebo (AR for mortality: 16/55 [29%] with pralidoxime *v* 3/55 [5%] with placebo; RR 5.3, 95% CI 1.7 to 17.3; intermediate syndrome: 36/55 [65%] with pralidoxime *v* 19/55 [35%] with placebo; RR 1.9, 95% CI 1.3 to 2.9; requirement for ventilation: 36/55 [67%] with pralidoxime *v* 22/55 [40%] with placebo; RR 1.7, 95% CI 1.1 to 2.4). [66] [67] However, baseline differences in this RCT suggested that more severely poisoned people might have been randomised to the intervention arm. [55] Reporting of methods in both RCTs was poor. In addition, both RCTs [65] [67] included in the review used doses of pralidoxime that were much lower than the regimen currently recommended by the World Health Organization (at least 30 mg/kg loading dose, then 8 mg/kg/hour iv infusion). [16] [68]

The second review [59] identified 7 clinical studies, three of which were in the first review, [58] and the third review [60] identified 6 clinical studies, two of which were included in the first review [58] and 5 of which were also included in the second review. [59] Both reviews performed meta-analyses, but included data from retrospective studies with historical controls and non-randomised controlled studies, a methodological weakness that makes interpretation of the results difficult. The first meta-analysis, which separated studies into retrospective and prospective study types, found limited evidence about the effect of oximes on mortality, need for ventilation, or development of intermediate syndrome compared with not receiving oximes (risk difference [RD] for mortality +0.09, 95% CI –0.08 to +0.27; RD for need for ventilation +0.16, 95% CI –0.07 to +0.38; RD for development of intermediate syndrome +0.16, 95% CI –0.12 to +0.45; absolute numbers not reported). [59] The meta-analysis found heterogeneity between study types but not within individual groups for mortality, but no heterogeneity for other outcomes. The second meta-analysis found limited evidence of worse outcomes for people treated with oximes (mortality: 43/162 [27%] with oximes *v* 19/167 [11%] with no oximes; RR 2.17, 95% CI 1.34 to 3.51; need for ventilation: 67/131 [51%] with oximes *v* 45/151 [30%] with no oximes; RR 1.53, 95% CI 1.16 to 2.02; intermediate syndrome: 52/110 [47%] with oximes *v* 30/92 [33%] with no oximes; RR 1.57, 95% CI 1.11 to 2.21). [60] However, the poor quality of all included studies in both meta-analyses suggests that the conclusion that oximes are not effective is unreliable.

The first subsequent RCT (21 people) of pralidoxime compared with placebo in people with organophosphorus poisoning found no significant difference in mortality, need for ventilation, or complications with pralidoxime, given at a dose of 4 g to 12 g infused each day over 3 days, compared with placebo (mortality: 1/10 [10%] with pralidoxime *v* 1/11 [9%] with placebo; P = 0.94; need for ventilation: 7/10 [70%] with pralidoxime *v* 4/11 [36%] with placebo; P = 0.12; complications: 4/10 [40%] with pralidoxime *v* 6/11 [55%] with placebo; P = 0.28). [61]

The second subsequent RCT (200 people with moderately severe poisoning with organophosphorus pesticide, intensive care unit in a private hospital in India, presentation within 24 hours, median time between ingestion and admission approximately 2 hours) compared a high-dose pralidoxime iodide infusion versus a standard bolus regimen (loading dose of 2 g over 30 minutes for both groups, followed by 1 g over 1 hour either every hour [study infusion group] or 1 g over 1 hour every 4 hours [control bolus group] for 48 hours, then both groups 1 g every 4 hours until people were weaned off ventilation). [62] Severely intoxicated people were excluded from the study. The RCT

found that high-dose infusion significantly reduced mortality compared with the bolus regimen (1/100 [1%] with high-dose infusion *v* 8/100 [8%] with bolus; RR 0.13, 95% CI 0.016 to 0.98; P = 0.035). It found that high-dose infusion significantly reduced the need for ventilation during admission (intubated during admission: 64/100 [64%] with high-dose infusion *v* 88/100 [88%] with bolus; RR 0.72, 95% CI 0.62 to 0.86; P = 0.0001). [62]

The third subsequent RCT (235 symptomatic people with organophosphorus pesticide poisoning, 2 Sri Lankan hospitals, median time since ingestion about 4.4 hours) compared saline placebo versus pralidoxime chloride (2 g loading dose over 20 minutes, then constant infusion of 0.5 g/hour until a maximum of 7 days, atropine had not been required for 12–24 hours, or death). [63] Randomisation was stratified by chemical structure (diethyl, dimethyl, unknown), time between ingestion and recruitment, admission severity, and allocation in a concurrent RCT of activated charcoal. It noted that local discussions of an earlier RCT, [62] which suggested marked benefits had resulted in loss of equipoise (the perception of treatments being of equal value) by clinicians, a fall in recruitment, and early termination of the trial. The RCT found no significant difference between pralidoxime and placebo in mortality, although mortality was higher with pralidoxime (deaths: 30/121 [25%] with pralidoxime *v* 18/114 [16%] with placebo; crude HR 1.82, 95% CI 1.01 to 3.28; P = 0.05; adjusted for stratification variables and intubation at baseline; HR 1.69, 95% CI 0.88 to 3.26; P = 0.12). [63] It found no significant difference between pralidoxime and placebo in the need for intubation post randomisation (26/121 [22%] with pralidoxime *v* 24/114 [21%] with placebo; crude analysis, HR 1.23, 95% CI 0.70 to 2.14; P = 0.47; adjusted for stratification variables and intubation at baseline, HR 1.25, 95% CI 0.68 to 2.27; P = 0.47; adjusted for baseline percentage aged acetylcholinesterase and plasma insecticide concentration, HR 1.80, 95% CI 0.83 to 3.88; P = 0.14). [63]

Harms:

Neither RCT included in the first review reported the incidence of adverse effects in people with acute organophosphorus poisoning receiving oximes. [64] [65] [66] [67] The second [59] and third [60] reviews reported no data on adverse effects occurring in the included studies, and the first subsequent RCT gave no information on harms. [61]

The second subsequent RCT reported that no substantial adverse effects (such as nausea, vomiting, or diastolic hypertension) were noted in trial participants; however, both diastolic and systolic blood pressure were significantly higher over the first 24 hours in the high-dose group compared with the standard bolus group (mean systolic [mmHg]: difference 20.6, 95% CI 19.0 to 22.2; mean diastolic [mmHg]: difference 8.3, 95% CI 7.2 to 9.5). [62]

The third subsequent RCT found that, compared with placebo, pralidoxime significantly increased tachycardia, hypertension, systolic blood pressure, and diastolic blood pressure after the loading dose at 20 minutes (all P values <0.0001), and significantly increased tachycardia at 72 hours (P <0.0001) and hypertension (P = 0.005). [62]

Adverse effects of oximes include hypertension, cardiac dysrhythmias (including cardiac arrest after rapid administration), headache, blurred vision, dizziness, and epigastric discomfort. [69] Such adverse effects with pralidoxime have been reported only with either rapid administration or doses >30 mg/kg bolus. It may be difficult to distinguish these adverse effects from the effects of organophosphorus. In one observational clinical study of a different oxime (obidoxime), a high-dose regimen (8 mg/kg bolus, then 2 mg/kg/hour infusion) produced hepatitis in 3/12 (25%) people. [12] Two of 6 deaths were because of liver failure. The use of pralidoxime (30 mg/kg loading dose, then 8 mg/kg/hour infusion) in 8 people in the same study did not produce hepatitis. A more recently developed oxime (HI-6) has also been used in humans, with no reported adverse effects. [70]

Comment:

Oximes (such as pralidoxime, obidoxime, and HI-6) reactivate acetylcholinesterases inhibited by organophosphorus poisoning. [13] [16] Reactivation is limited by ageing of the acetylcholinesterases and high concentrations of pesticides. Ageing of acetylcholinesterases takes longer with diethyl organophosphorus compounds than with dimethyl organophosphorus compounds. Oximes may therefore be effective if started within about 120 hours for diethyl organophosphorus poisoning and 12 hours for dimethyl organophosphorus poisoning. Treatment may be beneficial if continued for as long as the person is symptomatic because it may take several days for the pesticide concentration to drop below the point at which the rate of reactivation surpasses reinhibition. [13] In vitro and in vivo studies indicate that oximes can reactivate acetylcholinesterase; [13] [71] however, in vitro studies have also revealed mechanisms whereby oximes may be detrimental. [72] Thus far, clinical trials have not yet provided conclusive evidence concerning the clinical benefit or harm from oximes.

One RCT has been published, of a high-dose continuous infusion of pralidoxime iodide (1 g/hour) compared with an intermittent regimen of 1 g over 1 hour every 4 hours, both after initial stabilisation and an initial 2 g loading dose (see benefits section, above). [62] This RCT found that high-dose continuous pralidoxime reduced mortality, the need for ventilation, and risk of pneumonia. Of note,

this was the first RCT to have tested a dose of pralidoxime similar to that recommended by the World Health Organization. [73] One large prospective cohort study examining treatment with pralidoxime for 802 people with chlorpyrifos, dimethoate, or fenthion self poisoning found that acetylcholinesterase inhibited by the two dimethyl organophosphorus pesticides, dimethoate and fenthion, responded poorly to pralidoxime. [7] By contrast, acetylcholinesterase inhibited by the diethyl organophosphorus pesticide chlorpyrifos responded well to pralidoxime. [7] Further studies are required to determine whether this variation in response is true for all dimethyl and diethyl organophosphorus pesticides, and for higher doses of oximes. There have been no clinical studies of oximes in people poisoned by nerve agent organophosphorus compounds. These compounds differ in their rates of ageing, and compounds such as soman, that age rapidly, probably will not respond to the oximes currently available. [74]

Clinical guide:
There is currently mixed evidence regarding the effectiveness of the oximes, and some organophosphorus pesticides do not respond well to oximes. However, until the evidence base for oximes becomes clearer, it is difficult to contradict the World Health Organization guidelines to give high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hour or obidoxime 250 mg bolus followed by 750 mg/24 hours, both until at least 12 hours after atropine is no longer required) to all people with organophosphorus poisoning. [16] [68] One RCT comparing constant infusion with a bolus regimen found reduced morbidity and mortality in people with moderately severe poisoning. [62]

OPTION SODIUM BICARBONATE

We found no direct information from RCTs or cohort studies about sodium bicarbonate in people with acute organophosphorus poisoning.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found one systematic review (search date 2004) of sodium bicarbonate in people with organophosphorus poisoning, which identified no RCTs or observational studies of sufficient quality. [75]

Harms: The systematic review identified no RCTs or observational studies of sufficient quality assessing adverse effects in people with acute organophosphorus poisoning receiving sodium bicarbonate. [75] Dose-dependent adverse effects of sodium bicarbonate may include sodium and fluid overload and decreased oxygen delivery. [76]

Comment: Studies in animals found that increasing the blood pH with sodium bicarbonate (given orally or iv) reduced mortality from organophosphorus poisoning. [77] [78] This effect is independent of correction of acidosis because it is seen in animals that are not acidotic. Uncontrolled studies conducted in Brazil [78] and Iran [79] have claimed good results with sodium bicarbonate. Its mechanism of action in organophosphorus poisoning is unknown. However, it is unclear whether the limited increase in pH that is possible *in vivo* is sufficient to make a significant difference.

Clinical guide:
Currently, there is insufficient evidence to recommend the use of sodium bicarbonate in people with organophosphorus poisoning.

OPTION CATHARTICS

We found no direct information from RCTs or cohort studies about cathartics in people with acute organophosphorus poisoning.

Note
Organophosphorus poisoning itself causes diarrhoea, which can lead to electrolyte imbalance. This may be exacerbated by cathartics, suggesting that the risk of harm may outweigh their potential benefits.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality. Recognised complications of cathartics include electrolyte imbalance and dehydration. [80]

Comment: One non-systematic review identified no studies examining the effects of cathartics specifically in people with organophosphorus poisoning. [80] The review found no studies assessing clinical outcomes after cathartics in people with any other type of poisoning. [80]

Clinical guide:
Cathartics have been used to treat organophosphorus poisoning because they are believed to speed the passage of poisons in general out of the gastrointestinal tract. [80] Reduced transit time reduces the absorption of poison. However, organophosphorus poisoning itself causes diarrhoea, which can lead to electrolyte imbalance. This may be exacerbated by cathartics, suggesting that the risk of harm may outweigh their potential benefits. There is no reason to believe that cathartics will benefit people poisoned with organophosphorus pesticide.

OPTION IPECACUANHA (IPECAC)

We found no direct information from RCTs or cohort studies about ipecacuanha (ipecac) in people with acute organophosphorus poisoning.

Note
Administration of ipecacuanha may delay administration of activated charcoal and specific treatment for organophosphorus poisoning, in addition to increasing the risk of aspiration. Consensus is that ipecacuanha should not be given to people poisoned with organophosphorus pesticides.

For GRADE evaluation of interventions for organophosphorus poisoning, see table, p 17 .

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no studies of sufficient quality assessing the adverse effects of ipecacuanha in people with acute organophosphorus poisoning, and no large, high-quality RCTs comparing ipecacuanha versus placebo in any form of poisoning that might have allowed calculation of rates of adverse effects. Adverse effects of ipecacuanha may include aspiration, diarrhoea, ileus, dysrhythmias during vomiting, dystonia from treatment of vomiting, and haematemesis from vomiting. [81] Use of ipecacuanha in acute organophosphorus poisoning may be particularly hazardous because most organophosphorus compounds are dissolved in aromatic hydrocarbons, which cause serious harm if aspirated (see comment below). [81]

Comment: One non-systematic review, which included experimental and observational studies, identified no studies examining the effects of ipecacuanha specifically in people with organophosphorus poisoning. In people with other forms of poisoning, it found no evidence of benefit. [81]

Clinical guide:
Administration of ipecacuanha may delay administration of activated charcoal and specific treatment for organophosphorus poisoning, in addition to increasing the risk of aspiration. Consensus is that ipecacuanha should not be given to people poisoned with organophosphorus pesticides.

GLOSSARY

Acetylcholinesterase An enzyme that cleaves acetylcholine.

Atropinisation Giving atropine until it reaches a sufficiently high blood concentration to suppress cholinergic signs clinically.

Pro-poisons Some organophosphorus pesticides require activation in vivo to become toxic.

Ageing Esterases (such as acetylcholinesterase and neuropathy target esterase) are inhibited by organophosphorus compounds through phosphorylation. Inhibited acetylcholinesterase reactivates spontaneously at very slow rates; oximes speed up this reaction. However, phosphorylated acetylcholinesterase may lose an alkyl side chain non-enzymatically, leaving a hydroxyl group in its place ("ageing"). Regeneration is then no longer possible. The half-life of ageing is as fast as 8 minutes with the nerve gas soman but as slow as 33 hours for diethyl pesticides such as chlorpyrifos.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Rates of ageing The rate depends on the identity of the alkyl side chains on each organophosphorus. Those with two methyl groups will age faster than those with two ethyl groups and thus become unresponsive to oximes at an earlier time point.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Activated charcoal (single or multiple dose) New evidence added. [31] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effects of this intervention.

Atropine New evidence added. [18] Categorisation unchanged (Likely to be beneficial).

Gastric lavage New evidence added. [44] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effects of this intervention.

Oximes New evidence added. [62] [63] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effects of this intervention.

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Disclaimer

TABLE **GRADE evaluation of interventions for organophosphorus poisoning**

Important outcomes	**Mortality, pneumonia, intermediate syndrome, need for ventilation, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute organophosphorus poisoning?									
1 (39) [23]	Mortality	Glycopyrronium bromide *v* atropine	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events
1 (39) [23]	Need for ventilation	Glycopyrronium bromide *v* atropine	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events
1 (39) [23]	Pneumonia	Glycopyrronium bromide *v* atropine	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for small number of events and for proxy outcome (respiratory infection rates)
1 (1310) [31]	Mortality	Activated charcoal (single or multiple dose) *v* no charcoal	4	0	0	–1	0	Moderate	Directness point deducted for no overall analysis for organophosphorus poisoning alone (inclusion of carbamate pesticides in analysis)
At least 10 (at least 638) [59] [60] [61] [62] [63] [64] [65] [66] [67]	Mortality	Oximes *v* placebo or no oximes or different regimens *v* each other	4	–3	0	–1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results
At least 7 (at least 182) [59] [60] [64] [65] [66] [67]	Intermediate syndrome	Oximes *v* placebo or no oximes or different regimens *v* each other	4	–3	0	–1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results
At least 10 (at least 638) [59] [60] [61] [62] [63] [64] [65] [66] [67]	Need for ventilation	Oximes *v* placebo or no oximes or different regimens *v* each other	4	–3	0	–1	0	Very low	Quality points deducted for inclusion of observational data, incomplete reporting of results, and weak methods of included RCTs. Directness point deducted for lower than recommended dose used in some studies affecting generalisability of results

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.